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External Human Fertilization: An Evaluation of Policy

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Summary. In vitro fertilization, in its first 5 years of use, has met minimum standards for efficacy and safety, as judged by published clinical reports. It is becoming more widely available as an approach for overcoming sterility in married couples and appears also to be gaining social acceptance in that context. Several technical options presented by the procedure, particularly storage of frozen embryos and embryo transfers involving third-party contributions, are less fully evaluated clinically and raise social, ethical, and legal questions that go beyond the original medical model for therapeutic intervention. The clinical success of in vitro fertilization and the options it affords call for careful policy consideration. Estimates of costs and of potential demand for and supply of services are provided and the current status of relevant policy in the United States and abroad is discussed.

The first child resulting from fertilization of a human egg outside the body of its mother was born in England on 25 July 1978 (*1, 2*). An assessment of the clinical technology of in vitro fertilization (IVF) thus covers a 5-year period, although related laboratory studies had been under way much earlier (*3*).

Our objective is to offer an early appraisal of a procedure that has engendered significant controversy, both with respect to the procedure itself and to what can be viewed as an opening wedge to broader intervention in human reproduction, heredity, and development (*4*). A series of potential public policy questions can be envisioned that may strain the capability of existing decision mechanisms.

Since the initial clinical success in England, diffusion of the technology has occurred from the pioneer centers in England and Australia to the United States, Europe, and elsewhere (*5*). The diffusion is likely to continue during the next 5 years, as judged by the demand of sterile couples and the heightened efficacies reported by established centers (*6, 7*). In this article, we will address some of the derivative issues, indicate directions of current policy formation, and touch on the mechanisms being employed for policy decision. Some longer range options and appropriate oversight for such possible developments are also considered.

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Motivation, Efficacy, and Safety

In vitro fertilization falls within the realm of traditional medical motivation—to remove a limitation on normal healthy life. The specific initial objective was to overcome female sterility produced by absence or blockage of the fallopian tubes or oviducts, a condition estimated to occur in some 500,000 American women (*8*, p. 37). Since the oviducts are normal passageways for egg transport from ovary to uterus, as well as for sperm transport from the vagina and uterus to the egg, fertilization cannot occur without technological intervention. Surgical interventions have been practiced with some success, but there is a significant residue of cases in which surgery is unsuccessful (*9*).

The rationale for IVF and related procedures is to circumvent the block in the oviduct by (i) capturing the mature egg by laparoscopy just before it would be discharged from its follicle (ovulation), (ii) transferring it to a compatible external medium in which it can be exposed to sperm, (iii) allowing fertilization and early development to occur in the controlled environment of an incubator, and (iv) returning the egg to the natural internal environment beyond the oviductal blockage by inserting it through the cervix into the uterine cavity. The technology is theoretically as simple and direct as the motivation. Both the technology and the motivation, however, become more complicated as theory is turned into practice (*10*).

The intent of IVF is to provide a baby to an otherwise sterile couple. How well does the procedure accomplish its objective? Available published data (Table 1) (*11*), though still limited, indicate that efficacy has been significantly improving. For example, the first two births reported by Steptoe, Edwards, and Purdy (*12*) resulted from a series of 109 embryo transfers (the number of laparoscopies was not reported). This is a success rate (births per embryo transfer) just below 2 percent. The same clinical group (*10*, p. 414) more recently reported a series of cases involving 330 laparoscopies that resulted in 195 embryo transfers yielding 46 pregnancies. At the time of the report two babies had been delivered, and there were 29 stable pregnancies—an anticipated success rate of about 9 percent (births per laparoscopy). Other groups (Table 1) have reported similar rising success rates with increasing experience (*7, 13*). The clinical groups with greatest experience (Cambridge, England; Norfolk, Virginia; and two centers in Melbourne, Australia) have now formally reported series of cases with success rates for pregnancies per laparoscopy approaching 20 percent (*6, 7*).

Major technical modifications have also improved efficacy. For example, hormonally controlled cycles yield multiple instead of single mature eggs (*14*), incubation before fertilization permits full maturation of externalized eggs (*15, 16*), and transfer of more than one egg to the uterus increases the pregnancy rate (*6, 15*). Rates of success of egg recovery, of fertilization, and of achievement of early embryonic cleavage are each reported to be around 90 percent (*6, 17, 18*). The success of embryo transfer, however, is much lower (*6, 7*). For example, Table 1 shows a composite total of 1110 embryo transfers leading to 184 pregnancies—a success rate of nearly 17 percent. In contrast, estimates of success in the natural process suggest that roughly 45 percent of fertilized ova achieve implantation (*19*). Thus the success of embryo transfer in IVF is only about 40 percent that of the comparable phase in the natural process.

Among initial concerns about IVF (*20*) was the possibility of harm either to the potential offspring or to the mother. For the mother there are two identifiable risks—from the surgical procedures themselves or from the establishment of an ectopic pregnancy (outside of the uterus). Results to date diminish concern about surgical risk. Among more than 2000 laparoscopies for egg recovery, only a single event potentially affecting health or safety has been reported (*21*). This is a risk well within that of laparoscopy used for other purposes.

Published reports to date show two out of 184 IVF pregnancies that were ectopic (*22–24*). Although the number of IVF pregnancies is still low, the reported rate of ectopic pregnancy is within the range (0.3 to 3 percent) for the natural process (*25*). It also is below the recorded rate for pregnancies achieved following tuboplasty to overcome more complex forms of oviductal blockage (*26*).

Two concerns have been expressed about risk to the embryo—excessive death of early embryos and induced congenital abnormality in those born. It is clear that while the wastage rate is high in the normal process (*27*) it is even higher in the technology-assisted process. Estimates of the added deaths in the case of IVF must include both the high number of embryos lost during development of the technology and the lower number at its current level of efficacy. Evaluation of the excess of IVF deaths is complicated not only by the hotly debated issue of the status of the early human embryo but by the unresolved question of the percentage of the embryos that would have died anyway because of genetic or other defects. For the moment, it must be assumed that IVF has involved, and continues to involve, some unquantifiable cost in a higher rate of early embryonic death.

In the matter of induced congenital abnormality, there are likewise no certain conclusions. The number of IVF conceptions and births is as yet insufficient to detect statistically a small increment of abnormality above the natural rate (*28*). Several abnormalities of IVF embryos have been reported (*10*, pp. 343–349); neither in number or kind do they suggest that they were induced by the IVF procedure. Among approximately 125 IVF births (*19*), there has been only one abnormality reported (*29*), a cardiac malformation corrected by surgery. However, the earliest IVF children born are only approaching 5 years of age and subtle effects, such as neural defects impairing intelligence, might not yet be apparent. To summarize, there is no dramatic positive evidence reported for IVF-mediated damage to the more than 100 children estimated to have been born

Table 1. Summary of results from reporting IVF clinics. Successive entries for the same group represent more recent clinical series. Abbreviation: N.R., not reported.

Clinic	Laparoscopies	Embryo transfers*	Pregnancies	Efficacy (%)		Reference
				Pregnancies/laparoscopy	Pregnancies/embryo transfer	
Kershaw's Hospital, Oldham, England	N.R.	77	3		4	(*10*)
	65	32	4	6	13	(*10*)
Bourn Hall, Cambridge, England	330	195	46	14	24	(*10*)
Queen Victoria Medical Centre, Melbourne, Australia	112	218	16	14		(*31*)
	252		27	11	12	(*7*)
	90	70	25	28	36	(*56*)
Royal Women's Hospital, Melbourne, Australia	392	191	8	2	4	(*10*)
	N.R.	102	14		14	(*47*)
Eastern Virginia Medical School, Norfolk	40	9	0	0	0	(*6*)
	31	12	2	6	17	(*6*)
	24	19	5	21	26	(*6*)
	79	63	14	18	22	(*52*)
University of Kiel, Kiel, West Germany	185	19	2	1	11	(*10, 53*)
Hôpital Antoine Beclérè, Clamart, France	139	24	5	4	21	(*10*)
Hôpital de Sévres, Sévres, France	77	5	2	3	40	(*10*)
University of Southern California School of Medicine, Los Angeles	28	14	2	7	14	(*54*)
	16	11	3	18	27	(*54*)
University of Vienna Medical School, Vienna, Austria	65	19	4	6	21	(*10*)
University of Göteborg, Göteborg, Sweden	58	3	0	0	0	(*10*)
University of Adelaide, Adelaide, South Australia	54	27	1	2	4	(*55*)
Royal North Shore Hospital, Sydney, Australia	N.R.	N.R.	1			(*23*)
Total	2037	1110	184	8†	16.5	

*One or more embryos per embryo transfer. †Based on the 166 pregnancies achieved after 2037 reported laparoscopies.

to date. Furthermore, whatever the risk to either mother or offspring, it has not proved high enough to deter either the professionals or prospective subjects who are using the procedure in increasing numbers. In fact in March 1982 the board of directors of the American Fertility Society stated that under appropriate specified circumstances "in vitro fertilization must now be recognized as the acceptable treatment for achieving pregnancy for couples [in which the wife has] absent or irreparably damaged fallopian tubes" (*30*).

Feasible Extensions of the Basic IVF Procedure

When successful, IVF provides a child to a sterile couple. A number of possible variants of the basic procedure have been outlined (*4*), all well within technical capability but with quite different motivations and ethical, legal, and social consequences. These fall into several categories.

1) *Male infertility*. Several clinical groups are testing IVF involving male oligospermia—semen with low sperm count, low sperm motility, or other abnormality associated with infertility—and some success has been reported (*18, 31, 32*). The objective in this case is the same as that of the basic procedure—to provide a child to a sterile couple. New questions might be raised if the wife were fertile and IVF were performed on her to overcome a deficiency of her husband.

2) *Nonspousal sources of gametes (third party)*. Biologically it would be expected that egg and sperm from any two fertile members of the human species could be combined to yield an embryo. If the embryo is returned to the uterus of a married donor, use of sperm other than from her husband (if he is also sterile) is equivalent to artificial insemination by a donor (AID), a procedure that currently is countenanced but not encouraged in the United States. However, IVF also makes possible the converse procedure; that is, the egg might come from a female donor outside the marriage, and the husband might supply the sperm. The egg might be returned for gestation within the hormonally prepared uterus of the otherwise sterile wife. A rationale for such a procedure would be provided by a woman whose ovaries have been removed, but who has a normal uterus. The result of either IVF process, as in AID, would be a child genetically related to only one parent.

3) *Embryo transfer to a uterus other than that of the sterile donor*. The capability for embryo transfer to the hormonally prepared uterus of a nondonor of the egg makes possible several variants with different biological and social relations. The recipient might be a surrogate gestator who agrees to return the child to its genetic parents at birth. There is precedent for such surrogacy, by AID, to compensate for male sterility. The surrogacy option might also be applied simply to suit the convenience of the donor of an egg who did not want pregnancy but did want a child (analogous to wet-nursing). In another variation the recipient might be a woman who wants a child but without insemination, natural or artificial (*33*). In yet another variation, IVF might be used to yield a desired genetic combination without personal interaction, by combining egg and sperm from appropriate donors and transferring the embryo to a third party for gestation. This procedure would separate genetic selection completely from spouse selection and provide a technical base for human breeding programs.

There are few indications that efforts are being made to realize the options outlined above other than an interest [and an early report (*34*) from Melbourne (Queen Victoria Medical Centre)] in transferring "surplus" embryos from one treated couple to another sterile couple (embryo adoption).

4) *Freezing of embryos for storage*. This procedure is being performed by the Monash University Center in Melbourne, where a limited number of embryos have been frozen and viable ones transferred to a receptive uterus (*31*). A first success was reported as a 14-week pregnancy in early May 1983 (*35*). Freezing becomes an option because hormonal stimulation before laparoscopy yields multiple eggs that can be recovered in a single operation. This is advantageous because transfer of more than one embryo gives a higher pregnancy rate (*6, 15*), but also a higher twinning rate than normal, and because embryos not used in a first transfer attempt can be, if frozen and stored, used in a second transfer attempt without repetition of egg recovery.

However, if stored for longer periods, the embryos might constitute an embryo bank. It might, for example, be judged desirable to store embryos early in a marriage (not necessarily involving infertility) for use at some later times. This would provide the ultimate in family planning, as well as possibly allowing later childbearing without added risk of genetic defect (for example, Down syndrome). Success in identifying sex type in cattle embryos has been reported (*36*), and selection of sex of human offspring may not be far behind. Finally, embryo banks also make possible embryo adoption, if the genetic parents are willing to release the frozen embryos for transfer to other sterile couples or to any woman unable to bear her own child by the natural process.

A number of these extensions of the IVF process lie within the medical model—to correct disability limiting life or health, however these terms may be defined. Others, such as delayed embryo transfer for convenience, clearly go beyond the usual medical sphere. Also, in some of the extensions, such as embryo freezing, there may be added uncertainties as to safety and efficacy. Other species than the human appear to differ in their capability to withstand freezing (*37*), and there is little reliable information on possible sublethal damage that might become manifest subsequently in offspring.

Nonetheless, it is clear that all the extensions outlined above are within the present technical orbit—that is, if attempted, they are likely to yield some degree of success. In that sense they constitute a set of technological options ready for consideration for developmental trial. The set is not exhaustive since it does not include the possible application of several significant manipulations carried out successfully on mouse embryos at stages comparable to human embryos before transfer; an example is the insertion and expression of genes (*38*). Nor does the set include the possible development externally of human embryos to stages beyond those needed for transfer to the uterus. Such technical options would have to be undertaken, if at all, under rationales entirely different from those of the original medical impulse toward IVF. Nevertheless, the more direct IVF extensions seem already profound enough in ethical, legal, and social implication to warrant careful policy consideration. The process has begun in Australia and England, but in the United States there has been a hiatus since the report of the Ethics Advisory Board to the secretary of the Department of Health, Education and Welfare in 1979 (*8*). Several policy issues are discussed in the following sections.

Cost and Its Allocation

Information about prices charged to patients enrolled in IVF programs is relatively easy to obtain, but determination of the full actual costs of the services is

more difficult. The analysis below is based on data from the clinic at the Eastern Virginia Medical School in Norfolk, the first IVF program in the United States. The prices do not appear to differ substantially from those reported at other IVF centers, both here and abroad.

The basic charges to patients at Norfolk are $1650 for a preliminary screening procedure to establish feasibility of subsequent egg recovery, of which $400 is a professional fee and $1000 a hospital expense (Table 2). Charges for a subsequent attempt at egg recovery and embryo transfer, including hospitalization, are $3100—that is, a total of almost $5000 for a single complete treatment, whether or not successful. Excluded are such nonmedical costs as travel, lodgings, time lost from a job, and so on.

From the basic charges and information on home states of Norfolk patients, estimates of actual costs to patients can be made (Table 2). A typical total cost to the patient for an initial treatment (screening plus laparoscopy plus embryo transfer) is about $7500, with each additional attempt (omitting screening) costing about $5000. At current levels of efficacy, estimated from overall published data at roughly 10 percent for a given laparoscopy (Table 1), something of the order of $38,000 would be required to ensure a roughly 50 percent chance of a live birth for a particular patient (*34*). For each child born, aggregate costs are about $50,000, borne by both the successful and unsuccessful couples. It is not unreasonable to anticipate that the overall efficacy could double (*6, 7*), thereby providing a significant economic saving, as well as reducing discomfort and inconvenience for subjects. By rough estimate, such improved efficacy would also make IVF economically advantageous in comparison with more complicated types of tubal surgery (*5*).

Demand and Supply of Services

As more IVF centers are established in the United States (*40*), it seems important to develop an estimate of the likely demand for and supply of services. Data on infertility from the 1976 National Survey of Family Growth (NSFG) (*41*) show that about 380,000 married women between 15 and 44, who have had both of their fallopian tubes removed or tied, say that they would like to become pregnant. Adjustments for husband-wife concurrence and for reduced fertility in women over 35 lower the figure for actual candidates to roughly 150,000. In addition, both clinical (*42*) and survey data (*41*) indicate that about 850,000 other women have sufficient tubal damage to make pregnancy difficult, if not impossible. If 40 percent of these want children (a reasonable estimate based on the NSFG data), there are another 340,000 potential couples for IVF. If 15 percent of these achieve pregnancy without IVF, 290,000 candidates remain, and together with the 150,000 women without functional fallopian tubes, this constitutes a total pool of 440,000 potential couples for IVF. On the basis of a 12-year period of candidacy for IVF (for a woman between 22 and 34 years of age) and the assumption that each couple would seek only one child, there would be 36,000 candidates annually for IVF because of tubal problems alone.

Rough estimates suggest that if IVF were to be used for idiopathic infertility, oligospermia, and embryo transfers to nondonors the number of candidates might double, to 70,000 patients per year (*41, 42*). Because a pool of candidates has accumulated, the number seeking IVF is greater now than it will be when this pool is reduced. The percentage of actual candidates is, of course, subject to a number of factors, including insurance coverage, distance to a center, other treatment alternatives, and perceptions of IVF success rate. Because it is not possible to set precise values for any of these variables, we had to choose figures judged to be reasonable (*43*). For example, if 50 percent choose to attempt IVF the resultant estimated demand clearly is far greater than existing supply—defined as the capacity to deliver services by centers already initiated (see below).

Table 2. Cost estimates for the IVF procedure at Eastern Virginia Medical College, Norfolk. Transportation costs represent two round-trip tickets (husband and wife) from Chicago to Norfolk, the average travel distance for Norfolk patients. Lodging costs represent $30 per night plus $15 per day per person. The screening procedure requires 2 days each for husband and wife; the actual IVF procedure, egg recovery through embryo transfer, and monitoring for signs of pregnancy entails as many as 20 days for the wife and 2 days for the husband. On the basis of occupations of a sample of Norfolk couples, it is estimated that income is lost at a rate of $350 per week for the husband and $210 per week for working wives (approximately two-thirds of the wives are employed). The screening procedure entails the loss of 2 days wages for both husband and wife, while the remaining steps result in the loss of 2 days wages for the husband and as many as 15 days wages for working wives. If vacation or sick leave covers all lost wages for the screening visit and half the loss for the actual IVF procedure, total costs would be reduced by nearly $500. Deductability of medical expenses from taxable income will also reduce the cost to the couple.

Cost category	Cost of IVF (dollars)	
	Screening	Actual procedure
IVF program		
Administrative charge	100	
Andrology survey	150	
Laboratory		
General		850
Early pregnancy		500
Pergonal		250
Professional fee	400	1000
Hospital deposit	1000	1000
Transportation	500	500
Lodging	120	930
Lost wages	195	560
Total	2465	5590

In projecting the possible supply of providers, the first factor to consider is the attitude of specialists dealing with infertility, since establishment of an IVF clinic generally will begin with motivated physicians. Desire to improve treatment effectiveness, to increase income, to enhance prestige and opportunities for productive research are all possible motivations for physicians. Given the technical nature of the procedure, linkage between a clinician and a reproductive biologist is a strong advantage, if not a necessity. Required proficiencies for a team include (i) general medical, (ii) surgical including use of anesthesia, (iii) special skills with laparoscopy, endocrinological monitoring and embryo culture, and (iv) specialized nursing and technical support. In addition, access must be ensured to surgical suites on a priority if not dedicated basis. All of this points to advantages in associating IVF, as it is currently practiced, with large hospitals, particularly those connected with academic medical centers. Many early centers conform to this pattern. In addition, the practice of IVF in settings devoted to infertility will allow its advantages to be objectively evaluated and compared with other treatment.

What number of centers may be required and what criteria need be applied to ensure optimum care? Although it is too early to give definitive answers, it is not too early to pose the questions. Our estimates of demand, rough though they are, suggest that with availability of insurance 35,000 patients per year could seek treatment in the United States. The most mature IVF centers have between 200 and 400 patients per year; thus, about 100 centers could handle the estimated demand. Today there may be 10 to 20 established centers in this country, with an equal number in planning stages.

Therefore the character of the potential expansion can still be carefully considered so as to yield optimum services economically and therapeutically. No attempts along these lines appear to have been made.

If centers are designed to handle several hundred patients per year, experience at the two Melbourne centers indicates that a team of about 25 persons is required at each center (*31, 44*). But does the success of a center depend on such a large team and volume of patients? If it does, then the procedure might be carried out in academic medical centers alone (currently there are more than 100). This would have certain advantages initially—quality control, ease of continued research, and relation to other relevant medical expertise. It would also have disadvantages—exclusion of nonacademic practitioners, inhibition to miniaturization of the procedure, and excessive emphasis in residency training with possible overproduction of practitioners.

Were the procedure not limited to large centers and large volumes of patients, what then would be the optimum size and distribution of centers in terms of quality and economic considerations? What need is there for setting minimum standards for practitioners and groups? While accessibility of services (and hence certain costs) would be improved if centers were diversified in size and character to fit local circumstances, the problems of quality control would be considerably increased.

Current Status of Relevant Policy

The report of the Ethics Advisory Board (*8*, pp. 13–15) of the Department of Health, Education and Welfare (now Health and Human Services) provides a brief history of the beginnings of federal consideration of IVF. By August 1975 the department had issued regulations that included the following:

> No application or proposal (for research) involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been received by the [Ethics Advisory Board] and the Board has rendered advice as to its acceptability from an ethical standpoint.

There has been no further formal federal policy statement relating to IVF since 1975. Moreover, the advisory board was dissolved shortly after releasing its report in 1979. Accordingly, there is a de facto moratorium on federal support of IVF-related research but no other formulated governmental policy affecting the private sector either with respect to IVF research or practice.

Despite unofficial status, the recommendations of the Ethics Advisory Board are noteworthy since they suggest the kind of policy issues that are raised by IVF. The board's chief conclusions were (*8*, p. 100):

1) The human embryo is entitled to profound respect; but this does not necessarily encompass the full legal and moral rights attributed to persons.

2) The department should consider supporting animal experimentation relevant to IVF.

3) Research on human IVF is ethically acceptable, providing: regulations governing research with human subjects are complied with; the purpose of the research relates primarily to safety and efficacy of IVF; resulting embryos are not carried in the laboratory beyond implantation stages; the public is advised if risks of producing abnormal offspring through IVF exceed the normal; and all embryos transferred to the uterus are derived from married couples.

4) Proposed research on IVF-derived embryos for purposes other than relief of infertility should be referred for specific Board consideration.

5) The National Institute for Child Health and Human Development should take positive steps to collect national and international data on all aspects of IVF.

6) The Secretary should provide leadership to develop a model law on the legal status of IVF offspring.

The demise of the Ethics Advisory Board came shortly after the creation of the President's Commission for the Study for Ethical Problems in Medicine and Biomedical and Behavioral Research early in 1980. When asked by Senators Edward Kennedy and Orrin Hatch to comment on the six recommendations, the new commission responded that it was satisfied with the adequacy and thoroughness of the study, that the conclusions seemed well-supported, and that the commission might itself take up additional issues. However, at the time of its own termination of authority, in March 1983, the commission had not done so (*45*, p. 46).

No state has formulated policy specifically addressed to IVF. When planning began to establish the first IVF center in the United States at Norfolk, local groups opposed to IVF sought to block the effort. They were unsuccessful in getting any inhibitory action at either the local or state level. In Massachusetts a law (*46*) governing fetal research has been interpreted as possibly preventing IVF. A legislative effort to clarify the law to exclude IVF from possible proscription failed, and establishment of an IVF center in the state has been delayed by concern about prosecution under the fetal research law. In Tennessee, New York, Texas, and California, however, IVF centers have been established without challenge.

The practice of IVF primarily is spreading in the private sector and has apparently proceeded in ways that conform to the Ethics Advisory Board recommendations. This is not, however, the case abroad. In both Great Britain and Australia extensions of the basic procedure have been discussed and in certain instances, initiated. These developments have stimulated policy-making in each country that may be of interest in the United States.

Two independent centers in Melbourne, Australia, have put the city in the forefront of IVF practice in terms of numbers of patients treated and of births. Establishment of the centers was accompanied by considerable public discussion and controversy, eventually culminating in May 1982 in the formation, at the initiation of the attorney-general and minister of health of the State of Victoria, of a committee of citizens to consider the social, ethical and legal issues arising from in vitro fertilization. In part, the committee was formed in reaction to the policy of freezing extra embryos at one of the Melbourne centers and of the announced intention to make such embryos available, with the consent of the genetic parents, to sterile nondonor couples.

This citizen committee issued an interim report in September 1982 that contained a list of recommendations (*47*):

1) A campaign of public education on the nature, causes, and treatment of infertility should be initiated.

2) "Legislation to authorize hospitals as centers in which IVF programs may be conducted" should be enacted.

3) Evidence of 12 months or more of attempts to achieve pregnancy through "all other medical procedures" be required for admission to an IVF program.

4) IVF be limited to married couples, with all embryos returned to the donor.

5) Couples seeking IVF receive appropriate counseling.

The committee postponed making recommendations on freeze-thawing of embryos and their transfer to nondonors because disagreements among the members could not be resolved.

Meanwhile, the Australian National Health and Medical Research Council in September 1982 issued, on behalf of the federal government, revised ethical

guidelines for the research that it supports. The council stated (*48*) that IVF "can be a justifiable means of treating infertility" with the approval of institutional ethics committees and within an "accepted family relationship." Although it is assumed that the procedure would normally involve sperm and eggs from married partners, the guidelines allow for egg donation by another woman (AID analogue) and sanction research on embryonic stages prior to implantation so long as the donors give consent.

In England the course has been a little different. The clinical success of the pioneer efforts of Edwards and Steptoe was greeted in 1978 by great publicity and excitement. Although reservations of several kinds were expressed and no public support had been specifically provided, there was sufficient public acceptance to allow an enlarged and better designed center to be established later in Cambridge. Other centers have since been established by other groups (*10*). However, statements by Edwards to the press and in a scientific paper (*49*) about advantages to be gained by embryo-freezing and by the experimental use of embryos to improve and extend IVF led to renewed controversy. Prior to these events four study committees had been established to address concerns about IVF and possible research on human embryos. Two were created by medical professional groups (*50*), one by a private science and technology group, and one by the national government. The governmental report is expected in 1984.

In November 1982 the British Medical Research Council set out guiding principles for IVF (*51*); these are directed to its grantees but are likely to have implications beyond. The council sanctioned IVF research that is clinically relevant and involves no transfer of experimentally modified embryos for continued development in vivo. Informed consent from donors whose embryos may be manipulated is required. Surplus embryos from a therapeutic procedure may be used for experiments under the preceding stipulations. In addition, no surplus embryos may be cultured beyond the implantation stage and none may be stored (frozen) for unspecified research use. Experimentation on animal models is encouraged, and interspecific fertilization between human and nonhuman gametes is permitted as an aid to infertility studies, but no fertilized eggs thus produced may be carried beyond early cleavage.

In sum, it appears that as to efficacy, safety, and demand, the practice of IVF is moving toward or has already achieved established status as one therapeutic modality for human sterility. In Australia and Great Britain policy governing its use is actively being formulated; in several other countries, including the United States, application and development of the technique is proceeding solely on the initiative of health professionals and prospective patients. With few exceptions (none that we are aware of in the United States) the procedure is being applied only to married couples. Extensions beyond this, especially freezing of embryos and transfers involving third parties, are the subject of current study in Australia, England, and possibly other countries.

The Policy Horizon

Each of the possible extensions of IVF use noted earlier (*4*, *49*) poses a somewhat different set of ethical, social, and political issues, and each therefore may constitute a different public policy problem. Moreover, the technical status of the several options varies, giving different estimated times at which each extension may become feasible. Thus, embryo freezing and storage is imminent technically whereas safe and successful genetic intervention in embryos, if it ever will be desirable, is technically some distance into the future. The policy problem is how to cope effectively with a series of sequential challenges to current practices and the resultant stresses on the mechanisms of policy formulation.

The problem is not too different from and indeed overlaps that recently considered by the President's Commission for the Study of Ethical Problems (*45*), which pointed to a number of anticipated impacts of rapidly growing knowledge of molecular genetics: production of drugs and biologics, cancer diagnosis and therapy, genetic screening and diagnosis, and the curing of genetic disorders. With respect to the last, the commission distinguished between genetic intervention in somatic and germinal cells, the latter case being possible by intervention in embryos (referred to as "embryo therapy"), and noted the uncertainties about both the feasibility and desirability of such therapy.

In surveying the range of possible applications of molecular genetics the commission called attention to the breadth and variety of concerns that are raised, more than enough to defy "a simple arithmetical calculation" (*45*, p. 51) (for example, cost-benefit or risk-benefit analysis). After spelling out the multiplicity of concerns, the commission turned to protecting the future. It suggested that suitable oversight is required by "an evaluation process that is continuing rather than sporadic," allowing "the review body to develop coherent standards and orderly procedures, while making provisions for unexpected development . . ." (*45*, p. 82). Moreover, the commission envisions a requirement for "a process that is broad-based rather than primarily expert" because the issues will not yield to technical considerations alone and because the experts are likely to have a conflict of interest as "researchers or even as entrepreneurs" (*45*, p. 82). An oversight mechanism is called for that is primarily educational both for the public and the scientific community, that can exert leadership within the federal government, that is sensitive to public attitudes, that is scientifically well informed and that can exercise oversight without conflict of responsibility for "sponsorship."

Since oversight increasingly seems to be needed for the entire range of potential interventions in human reproduction, a continuing forum at the national level for study and deliberation on such interventions in both heredity and development should be helpful. In whatever form the forum emerges it certainly should update the 1979 report of the Ethics Advisory Board (*8*) regarding IVF. Moreover, since IVF overlaps and raises issues comparable to those involved in human genetic intervention, a single forum might deal effectively with both. The forum, as the presidential commission report (*45*) notes, could have several alternate organizational forms. The essential step seems to be to initiate the process, modifying it later as necessary to fit the course of events.

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Improving R&D Productivity: The Federal Role

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Today more than ever, now that everyone is focusing on productivity improvement, we should not forget the need for increased R&D productivity, especially in the billions invested by the private sector to use knowledge created by scientists. With the government spending some $47 billion a year on R&D, it seems to me penny-wise and pound-foolish not also to invest in evaluation, integration, and end user packaging of this knowledge produced at federal expense so that it can and will be put to use by the private sector. More effort in this area would greatly enhance the leverage of economic benefits from the federal government's investment.

Data and access to data are critical to every R&D project. Recently, in checking our own experience, I discovered that, in one typical IBM laboratory and plant library, 25 percent of the reference collection is primarily concerned with scientific and technical data. Some 15 percent of the volumes in circulation and over a third of the journals deal heavily with numeric data. This is a very heavily used collection.

When accurate, pertinent data are available, work can proceed. When they are not, work must stop while a researcher invents a different approach, develops (or redevelops) missing data, or experimentally verifies unevaluated data reported in the literature before daring to commit another period of time and effort on a project that is heading down a critical path.

Progress is not made by stopping work, or by shifting the goal away from the one you must achieve toward the one you can achieve. That is a good practice in research but a terrible way to do business. There is no way to measure this loss in R&D productivity—the cost in problems not pursued because they are unpursuable, or in new knowledge delayed—but the cost of the present policy is obviously high.

As materials science and process technologies mix with piece-parts assembly in high-technology manufacturing, we will see a whole new wave of industry requirements for basic scientific data. In this case, the requirements read directly on manufacturing effectiveness and productivity, as well as on the R&D process that most people associate with science and technology data.

Getting a product out the door is no longer a simple linear process, if indeed it ever was. Ideas do not necessarily originate in research and flow to development, to manufacturing engineering, to production, and to marketing. The relationship we now confront is a triangular one among partners in research, development, and manufacturing. It is not unusual today in my company to find

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